CMA
CHEMICAL MANUFACTURERS ASSOCIATION

April 29, 1996

Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room G-099
401 M Street, SW
Washington, DC 20460

ORIGINAL

Contains No CBI

8EHQ-0496-13636

ATTENTION: TSCA 8(e)

Dear TSCA 8(e) Coordinator:

The Cyclohexane Panel of the Chemical Manufacturers Association (CMA) hereby submits information on cyclohexane (CAS No. 110-82-7), which EPA may regard as reportable under provisions of TSCA 8(e). This information is derived from two studies conducted under the Testing Consent Order for cyclohexane (59 FR 59660, November 18, 1994; OPPTS 42094C). The two studies include a subchronic inhalation study with mice, and a subchronic neurotoxicity inhalation study (functional observational battery, motor activity, and neuropathology) with rats. When complete, final reports for these two studies will be submitted to EPA.

MICE

In the subchronic inhalation toxicity study, four groups of male and four groups of female mice (20 mice per sex each for the control and high-concentration groups, and 10 mice per sex each for the low- and intermediate-concentration groups) were exposed to 0, 500, 2,000, or 7,000 ppm cyclohexane. Exposures were six hours per day, 5 days per week, for a total of 66 exposures per sex over a 14-week period. Mice were observed weekly for clinical signs before exposure and daily after each exposure. Group clinical signs and the response to an alerting stimulus were determined during each exposure in animals visible from the front of the chamber. Approximately half of the mice could be observed in each chamber during exposure.

During daily observations of animals while they were in the chambers, abnormal behavior, interpreted as a potential neurological effect, was observed in mice exposed to 2,000 and to 7,000 ppm cyclohexane in a dose response fashion. Observed signs included hyperactivity in one or two mice visible from the front of the chamber in the 2,000 ppm group, and hyperactivity, circling, jumping/hopping, excessive grooming, kicking of rear legs, standing on front legs, and occasional flipping behavior in mice exposed at 7,000 ppm. In the 2,000 ppm group, hyperactivity first became apparent during the 64th exposure and continued until the end of the study. Abnormal behavior in the 7,000 ppm group was evident by the 4th exposure and continued throughout the remainder of the exposures. In addition, a diminished to absent alerting response was observed in mice exposed to 2,000 and 7,000 ppm cyclohexane.

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This altered alerting response was first observed during the fourth exposure in both the 2,000 ppm and 7,000 ppm exposure groups. These effects last a few minutes post exposure, and were not present the following day at the start of the next exposure. None of these effects were seen in the recovery groups.

Clinical signs of toxicity observed immediately after exposure in mice in the 7,000 ppm group included hyperactivity (4/40), hyperreactivity (16/40), gait abnormalities (3/40), spasms in both rear legs (3/40), and excessive grooming (2/40). Clinical signs of toxicity were first observed after the 15th exposure then continued in a sporadic manner throughout the remainder of the exposure period.

No behavioral or alerting response effects occurred at 500 ppm. No significant histopathologic findings were found in treated animals of any of the three exposure groups.

Similar behavioral effects (circling behavior and jumping movements) were reported in mice in the two-week range-finding study with cyclohexane. Behavior was affected at 6,000 and 9,000 ppm during exposure; however, no abnormal behavior was observed after exposure.

RATS

In the subchronic inhalation neurotoxicity study, 12 rats per sex per group were exposed to 0, 500, 2,000, or 7,000 ppm cyclohexane for 6 hours per day, 5 days per week, for 13 weeks. The response of the animals to an alerting stimulus (a standardized noise caused by striking the metal test chamber with a metal object) administered during each exposure period was evaluated and recorded. Because all of the animals were not visible through the chamber window during evaluation of the alerting response, it was not possible to quantify the number of animals in each chamber that responded; rather, the judgment about the reaction of the group as a whole was recorded. Approximately half of the rats could be observed in each chamber during exposure. A functional observational battery (FOB) and motor activity evaluations were conducted prior to initiation of exposure, and after 4, 8, and 13 weeks of exposure. After at least 65 exposures, animals were perfusion fixed, and nervous system tissues were evaluated microscopically.

The results of the FOB, motor activity, and neuropathological evaluations did not reveal any adverse, compound-related effects of cyclohexane exposure. During exposures, the alerting response of rats exposed to 500 ppm was judged by study technicians to be normal relative to control rats on each of the 69 exposure sessions. Rats exposed to 2,000 ppm exhibited a normal alerting response during the first four sessions, a diminished response during 31 sessions, and no response during 34 sessions. Rats exposed to 7,000 ppm did not respond to the alerting stimulus during each of the 69 exposure sessions. The diminished or absent alerting response is interpreted to be a compound-related sedative effect. The finding is related to previous evidence that exposure to 6,000 ppm, 7,000 ppm, and 9,000 ppm cyclohexane can induce sedation in laboratory animals. The sedative effects detected during exposures in this study were transient in that no clinical observations of compromised neurological function were detected when the rats were examined immediately upon removal from the exposure chambers. The absence of compound-related effects during the FOB, motor activity, and neuropathology tests further support the conclusion that cyclohexane-induced sedation during exposures to 2,000 ppm and 7,000 ppm should be regarded as a transient and rapidly reversible

phenomenon. The findings reported here are not remarkable, and sedative effects in animals exposed to such high levels of organic solvents are commonly observed.

The seven member companies of the CMA Cyclohexane Panel on whose behalf this submission is being made include:

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If you have any questions regarding this letter, please contact Jonathon T. Busch of my staff at 703/741-5633.

Sincerely,

Langley A. Spurlock, Ph.D., CAE
Vice President, CHEMSTAR

cc: Cyclohexane Panel
Cyclohexane Toxicology Research Task Group
John Harris, EPA
Director, Office of Compliance Monitoring

Triage of 8(e) Submissions

Date sent to triage:_____ NON-CAP CAP

Submission number: 13636 A TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Gordon Cash (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 -HERD (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.):_____

Notes:

☑ This is the **original** 8(e) submission; refile after triage evaluation.

☐ This **original** submission has been **split**; rejoin after triage evaluation.

☐ Other:

Photocopies Needed for Triage Evaluation

entire document: 0 1 2 3

front section and CECATS: 0 1 2 3

Initials:_____ **Date:**_____

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ-0496-13636 SEQ. A

TYPE: (NT) SUPP FLWP

SUBMITTER NAME: Chemical Manufacturers Association

SUB. DATE: 04/29/96 OTS DATE: 04/30/96 CSRAD DATE: 07/11/96

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
110-82-7

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	(01) 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
(0214)	SUB CHRONIC TOX (ANIMAL)	(01) 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	MUS RAT	(LOW) Ac. der., ac. oral		
CAS SR	NO	NO (CONTINUE)		(MED) Ac. oral, ac. der.		
	UNKNOWN	REFER		HIGH		

COMMENTS

13636A

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Subacute inhalation toxicity in the mouse and rat is of low concern. Mice (10/sex/concentration) and rats (12/sex/concentration) were exposed whole body to concentrations of 0, 500, 2000 or 7000 ppm (20 mice/sex at highest concentration) for 6 hours/day, 5 days/week for 14 weeks in mice and 13 weeks for rats. No deaths occurred for either mice or rats. No signs of neurotoxicity were observed in either species at 500 ppm. During and for a short time after exposure at 2000 ppm, mice exhibited hyperactivity and a diminished alerting response. Additional neurotoxic signs seen in mice at 7000 ppm included circling, jumping/hopping, excessive grooming, kicking of rear legs, standing on front legs, and flipping. No treatment-related histopathologic changes were seen in mice at any concentration. Rats at 2000 ppm showed a progressive lack of alerting response with successive exposures. Rats at 7000 ppm had no response from the first exposure; however, after cessation of exposure, rats exhibited normal neurological function.